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CUSHING'S SYNDROME

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CUSHING[1] recognized all the important clinical features of the disease that now bears his name, in the 16 patients on whom he based his original monograph in 1932. One observation stood out clearly: spontaneous remissions occurred. One patient received no treatment. The complete remission in another patient cannot be ascribed, as it was originally, to roentgentherapy to the pituitary. The records* indicate that the dose was probably approximately 400 r, which is not enough to produce a therapeutic effect. Remission occurred after roentgentherapy in another patient for whom the dosage is not known, but in view of recent developments is unlikely to have been in an effective range.

We have since learned that the features of Cushing's syndrome can be produced in animals and in man by injecting corticotropin (ACTH) or 17-hydroxycorticosteroids. Although the clinical picture in many patients having Cushing's syndrome is that of pure cortisone-like effects, curious mixtures of these and of other effects are observed, in which some features may be absent or may be greatly exaggerated. It is not infrequent that a mixture of effects of various steroids is seen: androgenic effects, for example, being slight in some patients and severe in others. In patients having carcinoma of the adrenal, especially, the pattern of steroid excretion may show striking alteration as the disease progresses.[2] In general, it is recognized today that most of the features of Cushing's syndrome are due to the chronic effects of an excess of hydrocortisone, or in other words hypercortisolemia. It seems likely, however, that in some patients there may be changes directly traceable to an excess of pituitary hormones, the effects of which are not mediated by the adrenals.

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Pathogenesis

It is trite to say that little is known in regard to the fundamental cause of Cushing's syndrome. I shall, however, recapitulate briefly some of the outstanding points currently accepted in regard to adrenocortical control, which have a bearing on the output of adrenal steroids.

It is thoroughly established that ACTH is a major factor in stimulating the output of cortisone and corticosterone, and the administration of large doses of ACTH is accompanied by changes in the zona fasciculata and the zona reticularis.[3] One way in which ACTH produces its effects is by promoting biosynthetic hydroxylation reactions. These reactions are apparently due to an increase in the availability of a common cofactor, namely reduced triphosphopyridine nucleotide.[4,5]

The output of ACTH varies strikingly under the influence of a servo or feedback mechanism, depending on the amount of circulating cortisol (hydrocortisone). Normally, by this balance, deficiency of cortisol stimulates ACTH production, while excess of cortisol or other related steroids reduces ACTH and hence cortisol production to small amounts. In the absence of the anterior hypophysis, the secretion of cortisol is greatly reduced, but is not entirely suppressed.[6] Unless the adrenals are atrophied, injection of ACTH will almost immediately restore cortisol production.

In addition to a minimal activity, which appears to be autonomous, and an adrenal-pituitary feedback balance, the release of ACTH is under neural control. Harris,[7] in 1955, suggested that a neurohormone arising in or near the median eminence of the hypothalamus travels through the portal venous system[8] to the anterior pituitary, where it induces release of corticotropin. This neurohormone is termed "corticotropin-releasing factor" (C.R.F.). The mechanism may be excited by a great variety of stimuli. An extract of the median eminence which is free of ACTH has been shown by Royce and Sayers[9] to contain C.R.F. Other investigators[10-12] have also produced hypothalamic extracts that are capable of stimulating the production of ACTH both in vitro and in vivo. McCann and Haberland[12] demonstrated recently that lesions of the median eminence apparently prevent the production of C.R.F., as indicated by the fact that an operation blocks the ascorbic acid depletion of the remaining adrenal, which otherwise occurs after unilateral adrenalectomy.

The obvious question with regard to the pathogenesis of Cushing's syndrome with bilateral adrenal hypertrophy is: "What, if any part, of these mechanisms is at fault?" If the original concept is correct, an abnormally high concentration of circulating corticotropin should be demonstrable. Many attempts have been made to test this hypothesis and, until recently, almost no evidence has been found to support it. Sydnor, Sayers, Brown, and Tyler[13] found less ACTH in the blood of three patients with Cushing's syndrome, than in the blood of patients with untreated or treated Addison's disease. In 1954, Paris and associates[14] concluded

from their own study and from examination of the results of others that in Cushing's syndrome with adrenal hyperplasia there was no increase in circulating ACTH.

Recent reports have made it seem much more likely than has been thought for many years that the ACTH-producing mechanism is at fault. Several reports[15,16] of pituitary tumors that were found after adrenalectomy in patients having Cushing's syndrome have been published. It is impressive that although such tumors occur after total and sometimes subtotal adrenalectomy for Cushing's syndrome due to adrenal hyperplasia, they have not been observed after adrenalectomy in patients with metastatic cancer nor in those with spontaneous Addison's disease. This, then, seems to imply strongly that the pituitary is being affected abnormally in patients having Cushing's syndrome, and the possibility of neural stimulation of the pituitary comes to mind. In some patients with Cushing's syndrome the titer of ACTH in the blood is much higher than that found in patients with Addison's disease.[17,18] It would seem likely that this propensity to excessive production of ACTH antedated the adrenalectomy and was exaggerated by it. The fact that suppression of corticoid production by administration of steroids occurs less readily, or less completely, in a patient with Cushing's syndrome associated with hyperplasia than in the normal person, may also be interpreted as meaning that there is increased force behind ACTH production in this condition.

In 1959, Liddle and associates[19] published data that seemed to favor strongly the idea of the presence of pituitary hyperactivity in Cushing's syndrome. Using as a test the drug SU-4885, which inhibits 11-hydroxylation, they showed that there is reduced production of cortisol, which is a good pituitary inhibitor, and that this reduction is associated with an abnormal rise in 11-desoxycorticosteroids such as compound S. This effect probably is the result of release of excessive ACTH. In this test, seven patients with Cushing's syndrome due to adrenal hyperplasia responded excessively as compared to normal persons and to patients having Cushing's syndrome who had been successfully treated by pituitary irradiation. In the latter patients the pituitary presumably was unable to muster sufficient vigor to produce an excessive amount of ACTH.

Nelson, Meakin, and Thorn[16] demonstrated the presence of excessive amounts of ACTH in 9 of 10 patients in whom pituitary tumors were found after adrenal surgery for Cushing's syndrome. The concentration of ACTH in these patients was higher than that found in patients with Addison's disease. By their method, however, excessive ACTH was not detectable in patients with untreated Cushing's syndrome.

The fact that some patients with Cushing's syndrome are hyperreactive to ACTH has not been explained. Jailer, Longson, and Christy[20] believe that this hyperreactivity may be due to some other associated neural or pituitary factor. The possibility that abnormalities inherent in the adrenal cortex cause its hyperreactivity must be considered. If these abnormalities are the cause, patients with severe pituitary deficiency should be capable of maintaining adrenal hyperfunction

in Cushing's syndrome. Hamwi's[21] remarkable patient may be a case in point. The patient had severe florid Cushing's syndrome. At the first operation one adrenal and all but 2 gm. of the other were removed. The disease persisted. Treatment of the pituitary by roentgentherapy failed to produce improvement, and hypophysectomy was performed. At the time of operation, the sella turcica appeared to be completely emptied. The symptoms persisted and, several months later, the urinary hydroxycorticosteroids were at concentrations higher than 60 mg. per day. Another exploratory operation was performed and a 20-gm. mass of adrenal was removed, but the patient died because of an operative accident. Unfortunately, the completeness of the hypophysectomy was not proved by autopsy.

Possible mechanisms by which Cushing's syndrome may be brought about include: (1) stimulation from the hypothalamus via the pituitary to the adrenal cortex causing adrenal hyperplasia by ACTH or possibly some other similar factor,[22] (2) hypothalamic stimulation in addition to pituitary tumor, (3) autonomous pituitary tumor, (4) adrenal hyperactivity due to inherent adrenal abnormality as well as the known, (5) autonomous adrenocortical tumors.

Pathologic Changes

Atrophy of the paraventricular nuclei in the hypothalamus has been described[23] as occurring in patients with Cushing's syndrome. It is thought that this atrophy does not represent a primary causative lesion but is secondary to the effects of corticoids, since similar changes after ACTH or cortisone treatment have been described.[24] So far as I am aware, gross hypothalamic lesions have not been found to be associated with the disease. This may or may not be relevant, since the same lack of association is true of other diseases in which pituitary hyperactivity is present, such as exophthalmos of Graves' disease, and acromegaly. A similar situation apparently exists with regard to the hyaline basophilic changes in the anterior pituitary described by Crooke,[25] since these too occur in cortisone-treated patients.[26]

Adenomata, almost always too small to show evidence of sellar changes on roentgenograms, are present in about half the patients. They are usually stated to be basophilic,[27] though controversy still arises as to the type of cell.[28] Small adenomata of the anterior lobe occur in the absence of Cushing's syndrome[29,30] in roughly 5 per cent of pituitaries in which a search is made at autopsy. Such tumors are almost invariably benign. We have seen 1 patient with pituitary carcinoma among 85 patients with proved or suspected Cushing's syndrome. In some of these patients deep pigmentation develops.[31]

The adrenal glands are histologically abnormal in almost all patients with Cushing's syndrome. In most series, the clinical syndrome is associated with hyperplasia of the adrenals in approximately 75 per cent of the patients; adenoma is present in approximately 15 per cent, and carcinoma in 10 per cent.[27,32,33] Although adrenal adenomata are relatively common in association with Cushing's

syndrome in women, it is a curious fact that they almost never occur in men.

In some of the adrenals that are free of tumor and are normal in size, signs of cellular hyperplasia are evident, but occasionally no abnormality is seen microscopically. In some glands of normal size, there may be an abnormal gross appearance though the microscopic appearance may not be distinctly abnormal. In such glands, a relatively thick, brownish-yellow zone may be present, bordering close to the outer rim of the cortex.[34] How frequently this may be due to preoperative steroid therapy is not known. Increase in the weight of the adrenals may vary in this disease from an almost normal weight to the tremendous amount of 86 gm.[35] for a total weight of both glands.

The zona fasciculata appears to be the most hyperplastic; the zona glomerulosa frequently is little, if at all, affected, or it may be atrophied. The medulla also may appear atrophied. Cohen, Chapman, and Castleman[36] summarized their observations of changes in the hyperplastic glands of 12 patients as follows:

> The development of hyperplasia was traced from apparently early stages to well developed nodulation. . . . In its initial phase the process was characterized by increased thickness of the zona fasciculata at the expense of the glomerulosa and medullary region. Initially this occurred without increase in total gland weight above normal levels. Lipid distribution was similar to that of the normal control, but depletion of sudanophilic material and particularly cholesterol was more marked. Cellular atypism noted in a number of the hyperplastic glands was considered an indication of unusual stimulation.

Although menstrual disturbances and amenorrhea are present in the majority of women with Cushing's syndrome, few pathologic ovarian changes have been described. Morris and Scully[37] studied the ovaries in four women and found neither polycystic changes nor abnormal luteinization. Iannaccone, Gabrilove, Sohval, and Soffer[38] reported findings in the ovaries of 10 women with Cushing's syndrome, four of whom were postmenopausal, and the ovaries were no different from normal postmenopausal glands. In the six patients in the fourth decade of life, the ovaries showed a sharp decrease in all follicular activity, and simulated changes due to aging.

A fascinating feature of Cushing's syndrome is related to its appearance in malignant disease primary in various organs. These include bronchogenic carcinoma.[35,41-45] In some of the patients with bronchogenic carcinoma a more profound electrolyte imbalance is present than usually occurs in Cushing's syndrome. The changes may mimic those seen in primary aldosteronism, but in at least two such patients aldosterone excretion was found to be slight.[42,46]

Cushing's syndrome has also been seen in patients with ovarian neoplasms of various types. Parsons and Rigby's[47] patient had an anaplastic carcinoma, and Deaton and Freedman's[48] patient had masculinovoblastoma. Some ovarian tumors associated with Cushing's syndrome produce more masculinization than is usually seen in this syndrome. The disorder has also been described as occurring in

patients with thymic carcinoma.[49] Scholz and Bahn[50] reviewed 11 such cases briefly, and added one case. Cushing's syndrome has also appeared in association with pancreatic carcinoma, with metastatic carcinoma of the prostate, and recently in association with pheochromocytoma,[51] and with carcinoma of the thyroid.[52] It is interesting that the adrenal glands in patients with Cushing's syndrome associated with carcinoma elsewhere in the body are almost all enlarged and hyperplastic, but the weights vary widely.

In patients in whom Cushing's syndrome is associated with carcinoma that is primary in other organs, the concentrations of urinary 17-ketosteroids and corticoids may be greatly increased, sometimes to the concentrations commonly seen when adrenal tumor is present. In a patient of ours with probable thymoma, the concentration of urinary 17-hydroxycorticoids increased to 73 mg. per 100 ml., and that of the plasma corticoids to 60 mg. per 100 ml. Under such circumstances, the question of whether or not these neoplasms in some way sensitize the adrenal cells or produce a corticotropin, is among the many questions that remain to be settled.

The demineralization in patients with Cushing's syndrome, although generalized, affects chiefly the spine, which leads to compression deformities or fractures of the vertebrae, kyphosis, and shortened stature. The central portions of the vertebrae on roentgenograms appear extremely pale, and the line of calcification beneath the chondral plates stands out more clearly than normally. The intervertebral discs bulge, causing wedging or hourglass deformities of the vertebrae. The ribs and pelvis are affected, and fractures, often of a painless type, occur. The skull takes on a patchy or mottled appearance, the laminae dura may disappear and the clinoid processes may become so pale as to simulate the appearance of a pituitary tumor. The osteoporosis apparently is due not to acute catabolism but to the antianabolic effect of cortisol. This explains the fact that negative calcium balance cannot be demonstrated in the disease.

It is interesting that many years after a so-called "cure" of Cushing's syndrome and complete disappearance of back pain, the central portions of the vertebrae may remain osteoporotic, remineralization being limited almost entirely to the regions adjacent to the chondral margins.[53] Skeletal destruction is almost certainly intimately connected to the tendency to renal calculous disease. Renal calculi were found in 5 per cent of 100 patients reported by Sprague and associates.[54]

Exophthalmos in this condition was described by Cushing.[1] It has been reported by Plotz, Knowlton, and Ragan[27] to be present in 7 per cent of patients. We have not observed exophthalmos of consequence in any of our patients. Malignant exophthalmos has been reported by Morgan and Mason[55] as occurring in a patient who had Cushing's syndrome and agitated depression. The concentration of urinary 17-oxyhydrocorticoids was 21.4 mg. per day (as determined by the Reddy method), and the blood pressure was 175/120 mm. of Hg. At autopsy, no signs of thyroid abnormality were noted except for one microfollicular cyst.

The available explanations for the hypertension are not adequate. Sodium retention is named as a factor,[56] but in view of work in recent years this does not seem acceptable. As has been mentioned, hypernatremia is not usually associated with the hypertension of Cushing's syndrome. It is true that under experimental conditions in rats, doses of 2.0 mg. of cortisol resulted in an elevation of the blood pressure[57] and larger doses caused nephrosclerosis.[58]

Sodium appears to be a sensitizing factor in causing the hypertension of desoxycorticosterone (DCA) but not that of cortisol.[59] This difference has been sharply emphasized by Guillemin[60] who showed that in rats on a sodium-restricted diet, severe hypertension developed during cortisol therapy, while in DCA-treated animals under the same conditions it did not. The addition of sodium to the cortisone treatment actually decreased the responsiveness of the test animals.

It has been suggested, but not proved for Cushing's syndrome, that cortisol may sensitize the cells to epinephrine, so that a normal amount of the latter may under some circumstances bring about hypertension. It is impressive that some patients have extremely severe Cushing's syndrome without hypertension; the absence of hypertension suggests that factors besides cortisol are at work. In Skanse, Gydell, Wulff, and Koch's[61] remarkable patient, the blood pressure was 250/140 mm. of Hg when the disease was mild, and fell to 140/95 mm. of Hg as the disease progressed; this was accompanied by a reduction in cardiac size.

In some patients, all measurable evidence of Cushing's syndrome may disappear except the hypertension. It is commonly assumed that the remaining hypertension under these circumstances may be due to irreversible vascular damage, since extensive vascular and renal changes are well known to occur. According to Glenn, Karl, and Horwith,[62] such changes range from minimal to marked "... arteriolar thickening, fibrosis and hyalinization of the glomeruli, tubular degeneration and focal infiltration of inflammatory cells." Such renal changes[63] would seem to furnish a reasonable explanation for the hypertension that may persist in patients in whom Cushing's syndrome has been controlled, because hypertension occurs not only after subtotal adrenalectomy but may occur after complete adrenalectomy.

The negative nitrogen balance of Cushing's syndrome is thought to represent increased gluconeogenesis, and to contribute to the progress toward diabetes mellitus but, as Ingle[64] has shown, it in no way explains it fully. Some degree of diabetes can be demonstrated by glucose tolerance tests in about 75 per cent of the patients having Cushing's syndrome, and this appears to be due, at least in part, to an interference with the action of insulin. Usually such diabetes is relatively mild, and for patients in whom insulin is required, dosages similar to those for the average diabetic patient are effective. In such diabetes there is little tendency to ketosis, greater than usual evidence of protein loss, and increased hepatic glycogen deposition, as well as a greater concentration of pyruvate and a lower concentration of phosphate than is found in the average patient with diabetes mellitus.[65]

Pronounced brownish hyperpigmentation of the skin and mucous membranes which occurs in some patients with Cushing's syndrome is of interest. Sulman[66,67] demonstrated, by testing human blood extracts in the tree frog, that there was an excess of chromatophorotropic hormone in three patients after adrenalectomy, in 25 of 30 patients with Addison's disease, in 15 of 45 patients with Cushing's syndrome, and in all three patients with Cushing's disease (pituitary tumor). He considered the test of value in designating which patients with Cushing's syndrome had pituitary tumor.

Few histologic studies have been made of the skin in Cushing's syndrome. My colleague, Dr. George H. Curtis[68] in the Department of Dermatology, has permitted me to quote some of his preliminary observations. "In general, the flattening of the epidermis with absence of rete pegs and papillae, edema of the upper corium, apparently increased but fragmented and frayed elastic fibers, and an apparent decrease of collagen and fibrous tissue, are distinctive features of the histologic changes in the skin from the forearm."

In some patients, there is a peculiar and unexplained disparity between some of the clinical and laboratory findings. Edema is a striking feature in some patients, but not in the majority, though electrolyte patterns and serum protein concentration may not differ, and urinary aldosterone may not be increased.[52]

Many of the symptoms can be accounted for on the basis of the protein antianabolic effect of corticoids. These effects include weakness and atrophy of muscles, thinning of the skin, osteoporosis and, probably, also a decrease in the power of wound healing.

I agree with Ragan,[69] and Frawley, Kistler, and Shelley[65] that there appear to be fairly constant differences between the spontaneous and the iatrogenic types of Cushing's syndrome. In most series of patients having the spontaneous type, arterial hypertension occurs in nearly 90 per cent, and some disturbance of carbohydrate metabolism is present in perhaps 75 per cent. In the therapeutically imposed type these features are rarely present.

In the presence of some diseases, such as lupus erythematosus, large amounts of cortisone or an equivalent drug may be administered over a period of months or years without producing the symptoms of Cushing's syndrome. As an example, one of our patients with lupus erythematosus was given treatment with corticoids from October, 1954, to the time of her death in May, 1960. Cortisone, in a dose of 100 mg. daily, or an equivalent of some other steroid, was used almost steadily from November, 1957, with no suggestion of the appearance of Cushing's syndrome, of hyperglycemia, or of hypertension.

Laboratory Tests

Tests most commonly employed in Cushing's syndrome have been those relating to the effects of: (1) stimulation with ACTH, and (2) inhibition of ACTH by administered steroids. These tests are of some value, not only in differentiating

patients with Cushing's syndrome from those with other diseases, but also in differentiating Cushing's syndrome due to hyperplasia and that due to neoplasm.

Among the many laboratory tests the results of which may be abnormal in Cushing's syndrome are those indicating erythrocytosis, lymphopenia, and eosinopenia. Hypernatremia is rare, but often alkalosis of the hypochloremic and hypokalemic types is present. The hypokalemia may be severe in the absence of a measurable increase in aldosterone.[52,70] In Hökfelt, Sjögren, and Falkheden's[52] patient, for example, there were spells of muscular weakness, polyuria, hyposthenuria, serum potassium concentrations of 2.2 mEq. per liter, and hypochloremia alkalosis; yet only traces of aldosterone were found in the urine, and none was detected in the adrenals.

It is equally fascinating that there are cases of Cushing's syndrome in which there are elevated values not only of urinary 17-hydroxycorticoids, but also of urinary aldosterone in amounts as great as 232 mg. per day.[71]

The most characteristic laboratory finding in Cushing's syndrome is an increase in the concentration of urinary 17-hydroxycorticoids. However, the amounts may decrease to within normal range when renal damage is severe.[72] The concentrations of urinary 17-ketosteroids in patients with hyperplasia may be normal or moderately elevated; frequently they are higher in patients with adenoma, and sometimes rise to extreme heights amounting to nearly 2.0 gm. per day in patients with carcinoma.[73]

In the presence of bilateral adrenal hyperplasia the response to ACTH is frequently greater, sometimes much greater, than normal. It is unfortunate for the diagnostic value of the test, that responses to ACTH much greater than the average normal response occur in a number of other conditions, including obesity, hyperthyroidism, hypothyroidism, hirsutism without other evidence of Cushing's syndrome in women, the last trimester of pregnancy, and the normal.[74] Even in Cushing's syndrome the results reported by various investigators appear to be at unexplained variance. The findings of Grumbach and associates,[75] of Christy, Wallace, and Jailer,[76] of Laidlaw and associates,[77] of Lindsay, Migeon, Nugent, and Brown,[78] and of Jailer, Longson, and Christy[20] seem to show a rather consistent hyperresponse to ACTH in patients having Cushing's syndrome; Bayliss and Steinbeck,[79] and Christy, Longson, and Jailer[80] found that prolonged administration of ACTH to normal persons did not cause an adrenal hyperresponse similar to that seen in patients with adrenal hyperplasia. Birke, Diczfalusy, and Plantin[81] found an exaggerated adrenal response in six of eight patients with Cushing's syndrome and hyperplasia.

Others[82,83] have found the response to be inconsistent. Jagiello[84] reported an increase of 25 mg. in urinary corticoids after intravenous injections of ACTH for two days in one patient having Cushing's syndrome, and a decrease in this value after two days of intramuscular administration of ACTH in another. Even more striking is the recent report of Dyrenfurth, Blair, Beck, and Venning[85] that there

was a much greater percentage response to ACTH in the specimens of urine from 21 normal subjects than in those from 14 patients with Cushing's syndrome. In their tests, four men with Cushing's syndrome showed an average increase of urinary corticoids of 38.9 mg. per day as compared to an average of 23.8-mg. daily concentration in the normal men, which is a considerable difference. In their series of 10 women with Cushing's syndrome, however, the increase in urinary corticoid output after stimulation averaged 18.9 mg. daily, as compared to an average of 17.7 mg. in the normal women. It is to be hoped that an adequate explanation of these apparent discrepancies will soon be forthcoming.

In persons having adenoma of the adrenal, the ACTH-urinary corticoid response is unpredictable: it may be slight, normal, or great.[77,78,86,87] In those having carcinoma of the adrenal this response usually is absent.

Among the most promising new diagnostic aids when uncertainty exists as to the presence of Cushing's syndrome are the suppression tests. A number of variations of this type of test have been reported by several groups over the past few years.[77,78,82,86-88] It seems reasonably certain that the adrenal is suppressed through inhibition of the pituitary ACTH-production, and therefore it is not surprising that adenomata and carcinomata usually behave autonomously and show little or no suppression as compared to the normal gland and to the hyperplastic gland.

The new and interesting test embodying partial adrenal suppression by SU-4885, has been mentioned.[19] Gold, Kent, and Forsham[89] have recently reported the use of the SU-4885 test in 10 patients with Cushing's syndrome. In six of these, proved to have adrenocortical hyperplasia, an abnormally high concentration of urinary 17-ketogenic steroids existed before the test. It was raised further by the administration of SU-4885 in all of them, and rose to even higher concentrations following intravenous administration of ACTH, and was suppressed by dexamethasone though not to low concentrations after doses of 8 mg. per day for three days. In two patients with benign adenomata and Cushing's syndrome there was no response to SU-4885, but a response to ACTH; while in two with carcinoma and Cushing's syndrome there was no response to either agent. In suppression tests, steroids commonly employed are Δ^1-9α-fluorohydrocortisol or its 16α methyl analog (dexamethasone). Jenkins and Spence,[90] and also Liddle[91] reported that the administration of these steroids in divided doses totaling 2.0 mg. per day produces almost complete suppression, measured as concentrations of urinary corticoids, in normal persons, and mild suppression in patients with Cushing's syndrome. In doses of 8.0 mg. per day the concentration of urinary corticoids in 35 patients with Cushing's syndrome and adrenal hyperplasia decreased to nearly zero; whereas, in 8 patients with adrenal tumor no such decrease in urinary corticoids appeared.

Prognosis and Therapy

It is well recognized that natural remissions in Cushing's syndrome do occur,

but they are not common. Plotz, Knowlton, and Ragan,[27] in studying the natural history of the disease, found that about half the patients died within five years after the diagnosis was made. In their experience, one of the leading causes of death was infection due to bacteria. This is not true today; now the chief cause of death is cardiovascular-renal disease. In our experience death has frequently been due to coronary artery thrombosis. Cerebrovascular accidents are also common. Unfortunately, myocardial infarction remains a likely cause of death when the disease, although apparently cured, has existed in severe form for some time. In our series, two men less than 40 years of age died from myocardial infarction after all major evidences of the disease were eliminated, and another young man had severe myocardial infarction but recovered.

When adenoma or carcinoma of the gland exists, removal of the mass is the only treatment that holds hope of effectiveness. Removal of a benign adenoma from a patient who has Cushing's syndrome of short duration produces a swift change toward normality and highly satisfactory results. In many, if not most, instances in which carcinoma of the adrenal exists, the carcinoma cells have already spread from the gland into the adjacent veins at the time the diagnosis is made.

There are two approaches to treatment of Cushing's syndrome with bilateral hyperplasia of the adrenals: (1) attack upon the pituitary, and (2) attack upon the adrenal. The pituitary may be treated by: irradiation; section of the pituitary stalk; partial or total removal of the pituitary; implantation of radon, gold, or more recently yttrium^{90} seeds, into the anterior lobe.

The first pituitary surgery for Cushing's disease was performed by Naffziger in 1933.[92] In his patient, remission lasted a year; subsequently the condition recurred and the patient died of Cushing's syndrome seven years after the operation. No autopsy was performed.

Luft, Olivecrona, Ikkos, and Hernberg[82] reported two patients operated on for Cushing's disease: in one patient, electrocoagulation of the pituitary was performed, and in the other, hypophysectomy. In both patients, the signs of the disease disappeared.

In 1938, Pattison and Swan[93] reported improvement after implantation of radon seeds in patients with Cushing's disease. Radon implantation was used by Northfield[94] in four patients: one patient improved dramatically; one improved slightly; one was not benefited; and one patient died. Successful treatment of Cushing's syndrome has followed the implantation of yttrium^{90} into the pituitary gland. This radioisotope would seem to be a particularly promising type since its beta rays extend such a short distance from the site of implantation. Complete regression of signs and symptoms after implantation of yttrium^{90} in two patients has been reported by Molinatti, Camanni, and Tedeschi,[95] and by Brooks, McSwiney, Mattingly, and Prunty.[96] In both of these patients the blood pressure reverted completely to normal, and in Molinatti, Camanni, and Tedeschi's patient, the daily concentration of urinary corticoids decreased from 30 mg. before treat-

ment to between 0.2 and 0.5 mg. two months after treatment, indicating that a rather severe pituitary insufficiency had ensued.

Roentgentherapy, and more recently cobalt[60] teletherapy, to the pituitary has been tried; good results have been reported in a number of patients, but the cure rate is not high.[97] Johnsen,[97] in 1952, reported the treatment of 12 patients with roentgen doses ranging from 6,000 to 16,000 r. Good results were obtained in 50 per cent of the patients. Three were considered definitely cured; the others had remissions, two of which lasted for three or more years. The experience of Dohan, Raventos, Boucot, and Rose[98] was approximately the same. Twelve patients were treated; results were excellent in five. The patients who showed the best results received doses ranging from about 4,000 to 5,000 r, over a relatively short period. Soffer and Gabrilove[99] also found that unsatisfactory results follow "extensive pituitary irradiation or pituitary irradiation and unilateral adrenalectomy" in more than half the patients thus treated. In the remainder, removal of most of the opposite adrenal is prescribed.

Today, adrenal surgery is the preferred method of treatment for most patients. Until a few years ago, the commonest form of surgical therapy was complete removal of one adrenal gland and removal of approximately 80 per cent of the opposite gland. Bilateral total adrenalectomy has frequently been advocated.[100,101] It has the advantage of producing an almost certain remission of the disease, but the disadvantage of imposing Addison's disease in place of Cushing's syndrome. Although severe adrenal deficiency can be treated effectively nowadays, there is still the undependable human element; and some patients with Addison's disease have died as the result of careless omission of treatment. There is also a risk because of the chance that sufficiently large doses of corticoids may not be quickly available in an emergency. In addition, the recent appearance of a number of postoperative pituitary tumors must be reckoned with, and these have occurred much more frequently in patients who have undergone bilateral adrenalectomy than in those who have undergone partial adrenalectomy.

When adrenal surgery is to be performed, the patient should be supplied with thoroughly adequate cortisone therapy: we usually prescribe 150 mg. per day intramuscularly for one or two days preoperatively; approximately 300 mg. intramuscularly in the early morning on the day of operation, and for one or two days postoperatively, diminishing to 50 to 25 mg. per day orally within a week, provided that the patient's condition appears to warrant it.

Mason, Richardson, and King[102] in discussing the matter of choice of partial or total adrenalectomy, state that in patients more than 45 years of age with slowly advancing disease, subtotal adrenalectomy is safer than total ablation and is adequate. They advocate a two-stage operation in these older patients, and recommend bilateral adrenalectomy in young patients and in those with rapidly progressing severe disease.

Postoperatively, it is well to supply each patient who has undergone adrenal

surgery with a card to be carried in his wallet, to certify in the event of an emergency that he has the approximate equivalent of Addison's disease. In addition to identification cards, our patients are supplied with two 100-mg. ampuls of hydrocortisone together with printed instructions to be kept near them at home or when traveling, for their use in case of emergency.

More long-term, careful, follow-up studies are needed after surgical treatment of Cushing's disease. The report of Cope and Raker[32] is interesting. Of 11 patients operated on for adenoma, one patient died after relief of the disease, and 10 patients were well at the time of the report. Of 27 patients with hyperplasia, operation was not performed in two, and they died of Cushing's syndrome. Two patients underwent partial resection and died of Cushing's syndrome. The 23 remaining patients underwent subtotal resection: four died of the effects of hypercortisolism; two died after a period of some relief; two were alive at the time of the report and still had Cushing's syndrome; and 19 were well.

Glenn, Karl, and Horwith[62] reported the results of surgical treatment in 30 patients. In their experience, unless the unilateral operation relieved the patient, bilateral adrenalectomy was performed. Thirty patients were operated upon; there were no operative deaths. In one patient with a small fragment of adrenal remaining, ophthalmoplegia developed from a pituitary tumor. Two patients subsequently went through normal pregnancy. One nine-year-old boy had no surgical treatment except a bilateral biopsy of the adrenal, and was in a complete remission at the time of the report. The remaining patients, seven years after operation, appeared to be doing well.

Estrogen therapy has been advocated but apparently is not effective.[103] Androgens have been highly recommended for their anabolic effect.[104] It appears that most physicians dealing with Cushing's syndrome do not depend on androgens as the sole method of treatment, but their value should not be overlooked as an adjunct to other forms of treatment in assisting with the repair of protein tissues and in the hope of repairing osteoporosis. The value of such therapy is not established.

Inhibition of corticoid secretion by amphenone has been reported by Hertz, Pittman, and Graff,[105] by Thorn and associates,[106] and by McCullagh and Tretbar.[107] Amphenone interferes with enzyme activity, blocking steroid synthesis, removing pituitary inhibition, and leading to adrenal hyperplasia.

Ortho p'D.D.D.[108] also is a drug that suppresses adrenocortical function. It appears to act as a rather specific cytotoxin to adrenocortical cells. This effect may be highly beneficial in some otherwise hopeless cases of adrenal cancer. Unfortunately, both amphenone and ortho p'D.D.D. are relatively toxic; they cause nausea, dizziness, and weakness suggesting a neurotoxic effect. They do, however, offer great hope that more practical effective compounds of a chemical nature may be found.[108]

It is hoped that in the future we may have not only agents that can be used

safely and efficiently to suppress adrenal function by direct action, but possibly also hormonal or chemical substances by which we may control adrenocortical steroid production by direct effects upon the anterior pituitary gland, or even upon the hypothalamus.

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FAMILY-CENTERED OBSTETRICS: AN EVALUATION

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IN 1956, the new section of obstetrics at the Cleveland Clinic afforded an opportunity to initiate a plan of obstetric care which incorporated certain features of other programs, as well as several innovations not previously reported. Complete obstetric care, we believe, includes not only the skill and equipment necessary to insure the safety of mother and child, but also the psychologic support necessary to make childbirth a satisfying emotional experience. Since all pregnant women do not require identical care, we maintain flexibility in our approach, and adapt our program to fit the individual woman, rather than have all women adhere rigidly to a standard program. Our belief that husbands should be considered full partners with their wives throughout the birth experience gives rise to the name *family-centered obstetrics.*

The Program

The three principles upon which our program is based are: prenatal education of both parents, participation of the husband, and permissive policies.

Prenatal education. The soundness of the principle of prenatal parent education is well established. It is recognized throughout the United States as a most important part of prenatal care.[1-4] Classes are conducted for groups of pregnant women and their husbands in which we offer seven lectures that cover the following general topics: (1) Anatomy and physiology of pregnancy, (2) Growth and development of the fetus, (3) Physical and emotional changes of pregnancy, (4) Proper diet and exercise, (5) Labor and delivery, (6) Newborn baby and layette, (7) Postpartum period. Husbands are invited to attend all the lectures with their wives, for they have correspondingly similar apprehensions and misinformation concerning pregnancy, based largely on superstition and old wives' tales. Forty-five per cent of our patients and their husbands attended the classes in the year just past, and an additional number had attended previous classes.

Just as education is of proved benefit to parents psychologically, the ability to perform certain exercises, especially certain breathing technics, is of value to a woman in labor. After the lecture by a member of the professional staff, a registered nurse instructs the class in the breathing technics and other exercises.

On the third Sunday afternoon of each month, an informal open-house reception is held at the hospital, at which time prospective parents are shown the hospital facilities, including the labor, delivery, and postpartum rooms. Familiarity with these rooms helps to dispel the anxiety concerning hospital procedures. Nearly

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all of our patients remark that the prenatal hospital tour makes their coming to the hospital easier.

Participation of the husband. It is our guiding principle that husbands be active participants throughout the birth experience. Some of the papers[2,4] reviewed on this general subject mention recommended attendance of the husbands at one or several lectures; a few mention their attendance during labor, but none record extensive experience with the routine attendance of the husbands at the delivery itself.

In our program, class attendance is not a prerequisite to attendance during labor and delivery, and it seems to make little difference except in the husband's comprehension of sequential procedures and, to some extent, his ease in participating. The presence of the husband throughout labor and delivery has proved to be of benefit to all concerned. To the wife, it means that she is never alone, an extremely important psychologic aid to the woman in labor. She receives the emotional support of her husband's presence, the physical support of counterpressure over the sacrum if low backache is present, and the encouragement to use the previously practiced breathing technics. To the husband, it means being a helpful participant, giving him a sense of being included in a major life experience. It certainly relieves the tensions, doubts, and fears that were expressed in former days by pacing of the floor in the hospital lobby. For the nurses, it means relief from the necessity of constant attendance at the bedside of the patient, since at no time are their patients alone, and attention will be given to immediate needs. The husband's physical assistance is often of benefit to a nurse in moving the patient in bed or from the labor room to the delivery room.

To the obstetrician, it is not only representative of good public relations, but it means he has an ally in the labor room—not an antagonist in the lobby. A little more of the obstetrician's time may be required with each patient in labor, but this is thoroughly consistent with good obstetric practice.

Inevitably, certain questions arise in regard to the presence of a layman in the delivery room. In many states, including the State of Ohio, persons not associated with the medical profession are barred from the delivery room by public health regulations. However, the Ohio State Department of Health has granted us permission to carry on our program and to evaluate the results. When present, the husband is properly gowned, capped, masked, and is seated at the head of the delivery table. A mirror is placed so that husband and wife may watch the baby's birth if they so desire. Contrary to the fears of some obstetricians, the presence of a lay person has not increased morbidity figures. Our over-all postpartum morbidity has been 2.6 per cent in the last year, most of which was due to cases of urinary tract infection or to superficial thrombophlebitis. Only two cases of endometritis developed, despite our standard procedure of performing intrauterine exploration after delivery of the placenta.

We believe that the presence of husbands has not interfered with our conduct of deliveries. Emergency situations such as hemorrhage or unexpectedly difficult deliveries are dealt with just as they would be were the husband not present. It is important that all personnel remain calm and composed under such circumstances, and often an emergency is over before the parents realize that one existed. Since most deliveries are entirely normal, the process is explained to the parents as it proceeds, and many parents have remarked that it is like watching a delivery on television, or like the movie that they had previously seen in the prenatal class. Fainting is practically unheard of, having occurred only once in our experience, when the husband left his seat and then tried to leave the room. The occasional fetal abnormality is described to the parents together, and they are informed of the proper corrective procedure. Often, in such cases, a plastic surgeon has seen the baby before it leaves the delivery room. If ever the husband's support is desirable, it is when a baby is anomalous or stillborn.

Permissive policies. There are many situations in which the patient may share in decisions that are made in regard to the conduct of her care. We have pointed out that although prospective parents' classes are offered to all patients and their husbands, not all husbands are able to attend. All husbands are invited to be present during labor and delivery, and 87 per cent of them have chosen to be present at delivery. We think that many of the ones who do not attend realize that they are not good subjects to observe the delivery, and it becomes a matter of self-selection.

The decision as to when analgesia is needed is left to the patient in normally progressive labor. She is instructed that medication is available at her request when she feels she is unable to remain relaxed. Under this policy, 33 per cent of multipara required no medication before delivery. The average dosages of meperidine hydrochloride and promethazine hydrochloride in combination were: 100 mg. of meperidine and 50 mg. of promethazine for primipara, and 50 mg. of meperidine and 25 mg. of promethazine for multipara. Although it cannot be claimed that little or no medication is requested, these doses are not large. In the postpartum period, standard medications are left at the bedside, and are taken as needed or as directed on individually labeled bottles. This policy of bedside self-medication has been previously reported.[5]

Visiting hours are maintained, but the number of visitors is regulated by the patient herself, who receives a booklet of passes through which she can control who may visit at each visiting period. It has been our experience that, with the patient controlling the visiting, most women come to realize the importance of adequate rest, and they themselves restrict visitors to a greater extent than if we were to lay down hard-and-fast rules. We are not constantly asked about special permission for out-of-town relatives, nor do we require police action by our nursing staff. Rooming-in may be elected, and peripheral nurseries are provided for

those who are interested. We do not encourage rooming-in until the mother decides she is able and eager to have the baby with her. In practice this most often has been on the fourth or fifth day postpartum; a seven-day over-all stay is recommended for the average mother and baby.

Results and Comment

The evaluation of an obstetric program such as the one we have outlined must take into consideration objective statistical data that lend themselves to analysis, as well as subjective elements that do not. The data covering only the last year of five years of experience with these methods are presented.

Groups 1, 2, and 3. The patients are divided into three groups, based on whether or not prenatal classes were attended, and on whether or not husbands attended labor and delivery of their wives. Group 1 comprises husbands and wives who attended classes, and the husbands were present during labor and delivery. Group 2 comprises those husbands and wives who did not attend classes, but the husbands were in attendance during labor and delivery. Group 3 comprises those husbands and wives who did not attend classes, nor were the husbands present during labor and delivery. Patients in whom induction of labor was carried out, whether elective or medically indicated, are excluded, as are those who required cesarean section.

There are 513 deliveries in the series. Of these, 231 couples (45 per cent) attended classes, but 450 (87 per cent) of the husbands chose to be present during labor and delivery. An analysis of the data in regard to analgesia, anesthesia, and length of labor is presented in *Tables 1, 2,* and *3.*

Table 1.—*Medication during labor*

Medication*	Number of Patients		
	Group 1	Group 2	Group 3
	Primipara (164)		
None	18	2	0
Single dose	45	17	6
Repeated doses	54	19	3
Total	117	38	9
	Multipara (349)		
None	54	51	15
Single dose	49	111	31
Repeated doses	11	19	8
Total	114	181	54

*Meperidine hydrochloride (dose, from 50 to 100 mg.), may be combined with promethazine hydrochloride (dose from 25 to 50 mg.).

Analgesia. Patients are instructed upon admission to the hospital that medication will not be given unless they request it, and their criterion should be their ability to relax during and between contractions. The initial medication is meperidine hydrochloride in from 50 to 100 mg. doses, frequently in combination with promethazine hydrochloride in from 25 to 50 mg. doses.

The most striking fact shown in *Table 1* is that 54 (47 per cent) of 114 of the multipara in group 1 (attended classes, plus participation of the husband) requested no medication before delivery; whereas, 51 (only 28 per cent) of 181 in group 2 (attended classes, but the husbands were not present at delivery)* received no medication before delivery.

We cannot substantiate the results of other obstetricians who have found that prenatal classes and orientation in natural childbirth and breathing technics have shortened labor and lessened the need for analgesia.[6] There is no significant difference in our groups, although it should be noted that average doses of drugs are relatively small *(Table 2).* The average durations of labor in primipara and multipara are close to those of other published statistics.

Table 2.—*Average total dosage of medication and average duration of labor*

	Group	Number of patients	Average dose of meperidine, mg.	Average dose of promethazine, mg.	Average duration of labor, hr.
Primipara					
	1	117	102	34	11.2
	2	38	112	44	10.4
	3	9	83	39	11.1
	Total	164			
Multipara					
	1	114	40	17	6.1
	2	181	55	25	6.5
	3	54	61	20	5.6
	Total	349			

Anesthesia. Conduction anesthesia is used in the vast majority of patients whether they are primipara or multipara, and regardless of whether or not they attended class or their husbands participate *(Table 3).*

Comment

It would appear from analysis of the foregoing data that our efforts have not been rewarded with remarkable alterations in the course and conduct of parturition. However, it is our belief that it is not of primary importance that we demon-

* should read: ...(did not attend classes, but husbands were present at delivery)
See Erratum, p 162, v. 29

Table 3.—*Anesthesia during delivery*

Type of anesthesia	Number of patients			Over-all percentage
	Group 1	Group 2	Group 3	
	(	Primipara	)	
None or local only	6	2	0	5
Spinal or caudal	105	37	10	95
General	0	0	0	0
Total	111	39	10	
	(	Multipara	)	
None or local only	31	21	12	18.2
Spinal or caudal	84	153	44	79.6
General	0	5	3	2.2
Total	115	179	59	

trate shorter time of labor or a greater incidence of spontaneous deliveries. The more important object is the development of a healthy attitude in the parents toward the child, toward each other, and toward future childbearing. We have not been able to evaluate this objectively, but we believe that from the enthusiastic response of those who participate, we are justified in continuing our efforts along the lines currently followed. We further believe that the molding of closer family units through such a program will contribute to their psychologic well-being and thus to stronger communities in general.

Summary and Conclusions

1. A program of obstetric care based on the principles of prenatal parent education, husband participation, and permissive policies is described.

2. No remarkable effect on length of labor, amount of analgesia, or type of anesthesia is demonstrable in the three groups of patients classified on the basis of degree of participation in the program.

3. Participation of husbands during labor and delivery is entirely feasible, is consistent with good obstetric practice, and offers important advantages to all concerned.

4. No attempt has been made to measure the immediate and remote psychologic advantages to the family unit, but the enthusiasm of patients assures us that continuation of the program is justified.

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A REVIEW OF OXYMORPHONE HYDROCHLORIDE (NUMORPHAN*) ANALGESIA EMPLOYED FOR GENERAL SURGERY

Including Clinical Experience With Five Hundred and Twenty-Eight Patients

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THIS paper presents a clinical evaluation of the synthetic analgesic, oxymorphone hydrochloride (Numorphan*), when used for preoperative medication, as a supplementary agent during general anesthesia, and for the relief of postoperative pain.

Chemical and Physical Properties of Numorphan

Numorphan hydrochloride is a colorless salt that has one molecule of water of crystallization. It is freely soluble in water and sparingly soluble in alcohol. The base melts in a temperature range from 248 to 249 C., and is readily soluble in acid and alkaline solutions. It is also soluble in chloroform and in acetone, and moderately soluble in ethanol and in benzene. The solution of the hydrochloride is stable at room temperatures and is not decomposed by light. It is miscible with atropine and thiopental and sodium without precipitation.

Figure 1 shows the chemical structure of Numorphan. It is an alkaloid, differing from dihydromorphinone by the addition of a hydroxyl group at the fourteenth position of the phenanthrene ring.

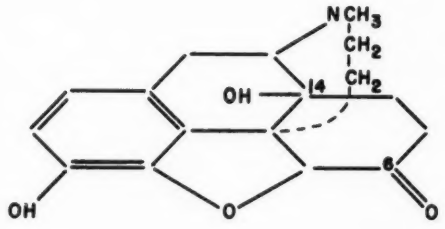

Fig. 1. Chemical structure of Numorphan (l-14-hydroxydihydromorphinone).

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Pharmacologic Properties of Numorphan Experimentally Deduced

In an experimental study Eddy and Lee[1] established that in humans, 1.02 mg. of Numorphan is equivalent to 10 mg. of morphine. Blumberg, Carson, and Stein[2] found that in mice doses exceeding therapeutic concentrations produced bradycardia. Blumberg and Carson[3] reported that Numorphan was not so constipating as morphine administered in equivalent doses. They[2,3] reported that N-allylnormorphine hydrochloride (Nalline*) reversed the respiratory depression induced by Numorphan.

It is postulated[4] that Numorphan possesses a certain amount of the so-called "tranquilizing" effect of such compounds.

Operative Administration in Humans

Previous clinical trials utilizing Numorphan indicate it may be sucessfully administered orally, rectally, or parenterally.

Preoperative medication. Numorphan as a preoperative medication was evaluated[5-7] when administered subcutaneously, intramuscularly, or orally in 513 patients. Coblentz and Bierman[5] commented on the absence of untoward side-effects, particularly of gastrointestinal disturbance, before and during surgery. They employed doses of 1 mg. of Numorphan with 0.4 mg. of atropine. In 38 patients who received intravenous injections of from 0.3 to 1 mg. of Numorphan in combination with 100 mg. of pentobarbital sodium two hours before operation, one patient had some respiratory depression; however, there was no evidence of respiratory depression in the other 37 patients, nor in those patients who received only Numorphan and atropine.[6]

McInnes, Engler, and Saliba[7] considered Numorphan to be a potent drug, with a low incidence of side-effects and offering a wide margin of safety. Appleton[8] prefers Numorphan as premedication before spinal analgesia or fluothane anesthesia.

Use during anesthesia. The use of Numorphan during anesthesia for operations on the head and neck was reported by Seigleman and Wasmuth.[9] They were impressed by the profound analgesia induced by this drug, and the patient's early return to consciousness and regaining of the vital reflexes. They also found a synergistic effect with thiopental sodium in producing respiratory depression, and used this to advantage. They augmented the analgesic action of Numorphan by hyperventilating their patients with nitrous oxide and oxygen mixtures; i.e., by creating a "narcotic-induced controlled apnea" similar to that produced by Foldes[10] with alphaprodine hydrochloride (Nisentil†).

Appleton,[8] on the other hand, purposely avoided the respiratory depressant action, when using the drug in combination with thiopental sodium, by reducing

**Nalline hydrochloride, Merck, Sharp & Dohme.*

†Nisentil hydrochloride, Roche Laboratories.

the dose of thiopental sodium to between 100 and 125 mg. He believed that the recovery time of the patient was prolonged when larger doses of thiopental sodium were used. When employing fluothane anesthesia, however, he noted that the narcotic action was useful in reducing the amount of fluothane required, and also for counteracting the tachypnea sometimes associated with fluothane anesthesia. He recommended that small increments (0.2 mg.) of the drug be administered intravenously during fluothane anesthesia.

Postoperative Analgesia

Numorphan also has been injected subcutaneously and intramuscularly for postoperative analgesia.[5] In 811 patients who received subcutaneous injections of from 0.5 to 1 mg. of Numorphan, effective analgesia was maintained for from three to six hours.[5] Other anesthesiologists[6] injected doses of from 0.5 to 1 mg. intramuscularly or subcutaneously into their patients, and found that adequate relief from pain was provided for from four to six hours. Appleton[8] employed intramuscular injections of Numorphan (from 0.5 to 1.5 mg. doses) during the recovery period, and noted that the patients were free from side-effects, especially nausea and vomiting, and also that a euphoria or a hypnosis was absent.

Methods of Our Study

Patients who received injections of Numorphan as premedication, during surgical operations, or during the recovery period, were carefully observed for the effects of the drug on cerebral activity, blood pressure, and respiratory and pulse rates. The occurrence of side-reactions such as nausea, vomiting, itching, or mental confusion were also noted and recorded. In addition, the drugs or anesthetic agents used in conjunction with Numorphan, the use of antidotes when required, the patient's physical state, and other factors such as loss of blood, were recorded and were taken into consideration in the evaluation of this drug.

Results

Premedication. Table 1 shows the results of the observations made concerning 66 patients who received premedication with Numorphan. In 18 of these patients the drug was injected intravenously; in 48 it was injected intramuscularly. Mental confusion, restlessness, and euphoria were absent, as were significant changes in blood pressure and respiratory rate. In six patients there was some itching about the nose. Nausea and vomiting were absent.

Use during anesthesia. In the patients in group A *(Table 2),* Numorphan was administered in conjunction with thiopental sodium, nitrous oxide, and oxygen, to produce a "narcotic-induced controlled apnea" as described by Foldes.[10] This group included the patients in whom this technic was used by Seigleman and Wasmuth[9] for surgical procedures involving the head and neck. The technic

Table 1.—*Use of Numorphan for premedication in 66 adults*

Drugs	Dose, mg.	Number of patients													
		Total	Sedation				Blood pressure change, mm. Hg			Respiration rate			Mental confusion	Itching	Nausea
			Good	Fair	Poor		+10	=	-20	+16	-14	-10			
Pentobarbital sodium	100	20	16	2	2		5	12	3	6	14	0	1	3	0
Numorphan	1.0														
Atropine (I.M.*)	0.4														
Numorphan	1.5	12	3	9	0		3	8	1	12	0	0	0	1	0
Atropine (I.M.*)	0.6														
Numorphan	0.75	16	2	10	4		4	12	0	16	0	0	0	1	0
Atropine (I.M.*)	0.4														
Numorphan	0.75	18	0	10	8		6	12	0	14	4	0	0	0	0
Atropine (I.V.†)	0.4														

*I.M. = Intramuscular injection approximately two hours preoperatively.
†I.V. = Intravenous injection from 5 to 10 minutes preoperatively.

the dose of thiopental sodium to between 100 and 125 mg. He believed that the recovery time of the patient was prolonged when larger doses of thiopental sodium were used. When employing fluothane anesthesia, however, he noted that the narcotic action was useful in reducing the amount of fluothane required, and also for counteracting the tachypnea sometimes associated with fluothane anesthesia. He recommended that small increments (0.2 mg.) of the drug be administered intravenously during fluothane anesthesia.

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			Good	Fair	Poor	+10	=	-20	+16	-14	-10			
Pentobarbital sodium Numorphan Atropine (I.M.*)	100 1.0 0.4	20	16	2	2	5	12	3	6	14	0	1	3	0
Numorphan Atropine (I.M.*)	1.5 0.6	12	3	9	0	3	8	1	12	0	0	0	1	0
Numorphan Atropine (I.M.*)	0.75 0.4	16	2	10	4	4	12	0	16	0	0	0	1	0
Numorphan Atropine (I.V.†)	0.75 0.4	18	0	10	8	6	12	0	14	4	0	0	0	0

*I.M. = Intramuscular injection approximately two hours preoperatively.
†I.V. = Intravenous injection from 5 to 10 minutes preoperatively.

Table 2.—*Use of Numorphan during anesthesia in 198 adults undergoing surgery*

Group	Anesthetic agents	Increment dose of Numorphan, mg.	Average total dose of Numorphan, mg.	Number of patients							
					B. P. change, mm. Hg			Respiratory rates			Nalline required, 5 to 10 mg.
				Total	+20	=	−20	+16	−14	−10	
A	Thiopental sodium (150-600 mg.) N_2O-O_2	0.375	1.375	62	10	50	2	7	30	25	30
B	Fluothane N_2O-O_2 Thiopental sodium induction (100-250 mg.)	0.375	0.75	53	2	36	12	70	33	0	5
C	Methoxyflurane N_2O-O_2 Thiopental sodium induction (100-200 mg.)	0.375	0.75	31	10	20	1	10	19	1	3
D	Cyclopropane Oxygen Thiopental sodium induction (100-200 mg.)	0.375	0.75	20	2	18	0	3	17	0	0
E	Spinal and	0.375	0.75	20	5	15	0	19	1	0	0
	epidural	0.375	0.75	12	5	7	0	11	1	0	0

included the reliance on respiratory depression and its potentiation by relatively large doses of thiopental sodium, together with the counteraction of such depression by the administration of Nalline. An average dose exceeding 200 mg. of thiopental sodium was administered to patients in group A.

In the patients in groups B, C, and D, who received intravenous injections of Numorphan to supplement anesthesia induced by inhalation agents, the average dose of thiopental sodium did not exceed 200 mg., and the incidence of noticeable respiratory depression was much lower. However, four patients required respiratory stabilization with intravenous injections of Nalline (from 5 to 10 mg.). Hypotension attributable to Numorphan was not encountered.

In patients in groups D and E, in whom Numorphan was used to supplement spinal and epidural anesthesia, there were no noticeable side-reactions, despite the

fact that premedication for most of these patients had included pentobarbital sodium (Nembutal*).

Postoperative observations. All the patients had satisfactory blood pressures and respiratory rates on admission to the recovery room *(Table 3).* No patient whose blood pressure was being supported by a vasopressor or a blood transfusion was included in this series.

Table 3.—*Postoperative observations in 264 patients receiving Numorphan**

	Number of patients										
		Pain relief			Duration		B. P. fall, minutes	Respiratory rate		Nausea and vomiting	Mental confusion
	Total	Good	Fair	Poor	30+ min.	2+ hr.	20 mm. Hg	16	10		
	26	12	6	4	20	6	0	2	0	4	1
	60	24	16	10	52	4	2	0	3	10	0
	40	14	10	16	6	2	0	2	0	10	0
	70	24	38	6	46	14	7	6	5	0	0
	28	20	8	0	28	12	2	0	0	0	0
	16	2	12	2	16	0	5	4	0	2	0
	24	14	2	4	16	0	2	2	0	4	0
Grand total	264	110	92	42	184	38	18	16	8	30	1

*Intravenous injection, 0.5 mg. to total of 2 mg., according to patient's age, weight, and severity of pain.

Each of the eight patients in whom there was gross depression of respiratory rate was more than sixty years of age, and had received total doses of more than 1.5 mg. of Numorphan during the recovery period. Administration of 5 mg. of Nalline reversed the depression rapidly and completely in each patient.

Although the 18 patients in whom a decrease in blood pressure was encountered had each received less than 1.5 mg. of Numorphan, it was believed that the drug may have been responsible for the hypotension. No related respiratory depression was apparent clinically in any of these patients. However, alveolar ventilation was not measured, and changes in plasma carbon dioxide content could have caused some of the alterations in blood pressure.

There was a significant absence of sedative and hypnotic effects, but in some patients (11 per cent) nausea and vomiting occurred which could not easily be attributed to factors other than the administration of Numorphan. All medication was injected intravenously, and this may in part account for the incidence of side-effects in our trial.

**Nembutal sodium, Abbott Laboratories.*

Summary and Conclusions

1. Numorphan is found to be a satisfactory narcotic for premedication, as a supplement to general anesthesia, and for postoperative analgesia.

2. It is not devoid of side-effects, the most undesirable effect being the depression of pulmonary ventilation. This reaction may be avoided to a great extent by reduction of the dosage of Numorphan, and may be counteracted by the injection of Nalline.

With certain technics of general anesthesia, central depression of respiration may be used to advantage as a means of instituting controlled respiration or for counteracting tachypnea. Vasomotor depression is not apparent even when relatively large doses of Numorphan are employed.

3. The potentiation of Numorphan by barbiturates is evident, and may be an advantage or a disadvantage, depending on whether or not it is intentional or inadvertent.

4. The absence of sedative effects and suppression of coughing, and the low incidence of gastrointestinal disturbance, make Numorphan valuable for premedication and postoperative analgesia. The drug may augment the action of sedative or tranquilizing drugs administered additionally, and the dose used should be adjusted accordingly.

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MASSIVE LOBAR EMPHYSEMA IN INFANTS: DIAGNOSIS AND TREATMENT

Report of Three Cases

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MASSIVE lobar emphysema in infants deserves more widespread recognition, because it requires emergency surgical treatment. The condition is readily diagnosed, and if untreated may prove fatal. Surgical removal of the involved lung tissue is lifesaving.

Diagnosis

The disease may be recognized clinically from the history, physical examination, and roentgenograms. In general the history is that of a baby who was normal at birth but in whom respiratory distress developed within the first few weeks of life. Often the respiratory distress is intermittent and is precipitated by feeding or by crying. It is characterized by dyspnea, wheezing, grunting, coughing, and cyanosis. As the disease progresses the dyspnea and cyanosis become profound and the infant may die of respiratory failure.

The physical findings are those of emphysema. The child breathes with difficulty with flaring of the ala nasi and retraction of the costal cartilages. Breathing is audibly difficult, and an expiratory wheeze is commonly heard. The breath sounds are diminished on the diseased side, sometimes having an amphoric quality. Crackling rales may be heard on both sides in addition to the expiratory wheeze.

Excitement, or the greater respiratory effort associated with feeding or crying may cause cyanosis. The portion of thorax over the involved side is more prominent than that over the uninvolved side. The excursion of the chest wall during respiration is limited. The percussion note is hyperresonant, although this fact may be difficult to demonstrate in the normally resonant infant's chest. Laryngeal stridor is not present. The heart is displaced to the side opposite the lesion, and the diaphragm is displaced downwards.

Roentgenograms show evidence of such severe emphysema that attention may erroneously be directed to the opposite side, and the diagnosis of atelectasis may

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be made. Usually there is atelectasis of the lobes adjacent to the emphysematous lobe. Often in addition to the displacement of the mediastinal contents there is herniation of the involved lobe across the mediastinum.

The differential diagnosis includes congenital cystic disease of the lung, pneumatocele, spontaneous pneumothorax, localized emphysema, generalized obstructive emphysema, aspiration of a foreign body, hyaline membrane disease, diaphragmatic hernia or eventration, and cyanotic congenital heart disease. Accurate interpretation of the roentgenograms will serve to differentiate most of these diseases. It is important to note the persistence of pulmonary markings in massive lobar emphysema, which are not present in congenital cystic disease of the lung, in pneumatocele, or in pneumothorax. There has been much unnecessary confusion between congenital cystic disease and lobar emphysema. Localized emphysema such as may be seen in association with cystic fibrosis of the pancreas may be difficult to distinguish from lobar emphysema until the primary disease has been recognized. Aspiration of a foreign body is rare in infants so young; hyaline membrane disease is rare in infants so old. Both diseases may be ruled in or out by the history and roentgenograms. The latter also serve to establish the presence or absence of diaphragmatic hernia. Congenital heart disease may be difficult to differentiate since it often is seen in association with massive lobar emphysema. When uncertainty exists, the clinician's problem is to decide which disease is most threatening to the life of the patient.

Treatment

The treatment of massive lobar emphysema in infants is always the surgical removal of the involved pulmonary lobe. This seems to be readily accomplished by skilled surgeons, even in the most desperate circumstances. Relief of the symptoms promptly follows removal of the lobe.

Pathologic Study

The surgically resected pulmonary specimen was studied in each of the three cases. In two instances the tissue was dissected in the fresh state and representative blocks were fixed in modified Zenker's fluid.* One specimen was fixed by instilling 10 per cent formaldehyde into it via the main bronchus to the lobe; representative blocks were then taken after fixation was complete. All sections were stained with hematoxylin-eosin and methylene blue stain. The fibrous tissue component of the representative blocks was assessed by means of Masson's trichrome stain, and the elastic tissue component was assessed by means of Verhoeff's elastic-tissue stain. Representative blocks, usually two to a lobe, were routinely taken, one from the hilar region and one from the peripheral portion

**Mercuric chloride, 3.5 per cent; potassium dichromate, 2.5 per cent; glacial acetic acid, 3 per cent; in distilled water.*

of the parenchyma. As control material, representative sections of necropsy specimens from infants of approximately the same age were compared with the sections for this study.

Report of Cases

Case 1. A three and one-half month old white male infant was first examined in September, 1954, because of "heart disease." The pregnancy and delivery had been normal, and the infant at six weeks of age was thought to be healthy when examined by his physician. When he was two months old, the parents noted episodes of heavy breathing after crying, but no cyanosis or coughing. On examination he was breathing rapidly with retraction of the sternal notch and lower rib margins. The respirations had an unusual stridulous quality not suggestive of laryngeal stridor. Scattered fine crackling rales could be heard at the end of inspiration, accompanied by some sibilant expiratory wheezes. The breath sounds were amphoric on the right side. The right side of the chest wall did not move with respirations. A grade 3 to grade 4 systolic bruit could be heard maximally over the left second to fourth interspaces. A systolic thrill could be palpated in this region. The pulmonic second sound was greatly accentuated. Fluoroscopy disclosed about 25 per cent over-all cardiac enlargement predominantly involving the right ventricular outflow tract. The mediastinum was displaced to the left and did not shift with respirations. The electrocardiogram revealed a sinus rhythm. The P waves were high and peaked in standard lead 2; they were notched in standard lead 1, and diphasic in leads from the right precordium. The R-R interval was 0.39 sec.; the Q-T interval, 0.27 sec. The precordial pattern revealed the presence of incomplete right bundle-branch block thought to be associated with right ventricular hypertrophy. Roentgenograms demonstrated evidence of an enlarged heart *(Figs. 1 and 2)*. There was notable emphysema of the right middle lobe, with partial atelectasis of the right upper and right lower lobes.

Cardiac catheterization was performed by Dr. F. Mason Sones, Jr., of the Department of Pediatric Cardiology and Cardiac Laboratory, through the right superficial femoral vein. A high interventricular septal defect was demonstrated as well as a patent foramen ovale. Significantly high right ventricular pressure essentially equal to the femoral arterial systolic pressure was present. Pulmonary venous blood returning from the left upper pulmonary vein and that in the left atrium demonstrated gross arterial oxygen unsaturation with only 84 per cent of capacity.

A thoracotomy was performed by Dr. Laurence K. Groves of the Department of Thoracic Surgery. The right middle lobe of the lung was greatly enlarged, and it would not collapse when positive pressure was removed via the anesthesia circuit or by direct finger pressure. Patchy atelectasis was present, particularly in the superior segment of the lower lobe and the posterior segment of the upper lobe. The right middle lobe was removed without difficulty; it was noted that the bronchial stump leaked little air even with positive pressure maintained by the anesthetist. The postoperative course was uneventful and the respirations were greatly improved.

The resected right middle lobe was 8.0 cm. by 6.5 cm. by 2.0 cm., and weighed 30.0 gm. *(Fig. 3)*. The general configuration was that of an overinflated or emphysematous

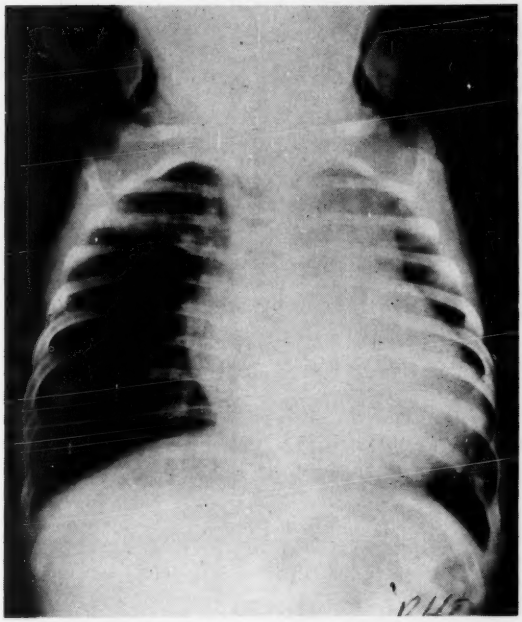

Fig. 1. Case. 1. Roentgenogram of the chest, demonstrating massive emphysema of right middle lobe with cardiac enlargement.

pulmonary lobe. Grossly the hilus of the lobe revealed no abnormality of the major bronchi or of the major pulmonary vessels.

Sections from the hilar area and from the periphery of the lobe showed dilatation of the tertiary bronchi and of the terminal bronchioles *(Fig. 4)*. The cartilaginous, muscular, and epithelial components of the tertiary bronchi and the terminal bronchioles appeared to be within normal limits. The pulmonary parenchyma showed so widely dilated an alveolar pattern, that alveolar ducts, alveolar sacs, and alveoli could not be separately identified. Many of the alveolar walls were ruptured, thus forming irregular, polyhedral, partially septated spaces. The septae in general were thin, and no significant inflammatory infiltrate was observed. The intraalveolar hemorrhage was thought to have been surgically induced. Since it was known that the bronchial stump had not leaked air during the operation, it was presumed that an obstructive lesion in the bronchus of the right middle lobe had been left intact at the time of the operation. The child was followed for two years as an outpatient. At the first examination four months postoperatively, dyspnea was absent, but the parents stated dyspnea had remained for some time after the child was discharged from the hospital. He had had two respiratory infections, in the interval, which were not unusually severe. On further follow-up examinations he was noted to have had a great number of respiratory infections, and his general growth and development were subnormal. Cardiac surgery was advised

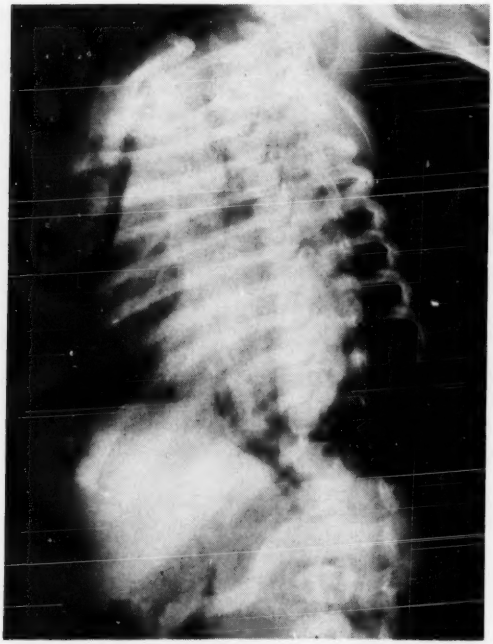

Fig. 2. Case 1. Oblique roentgenogram of the chest, demonstrating herniation of right middle lobe in the anterior mediastinum.

in 1956, but was refused by the parents. The patient has not been examined since that time.

Case 2. A three-week-old white male infant was first examined in November, 1959, because of cyanosis during crying. The pregnancy and delivery had been normal. The parents had noticed that the child was dusky when feeding, and breathed heavily. On physical examination the baby seemed critically ill. The lips, hands, and feet were cyanotic. The respirations were rapid and labored with retraction of the sternum. An expiratory wheeze could be heard. A systolic thrill was palpated over the precordium. The heart rate was 160, and a grade 4 systolic murmur was heard at the apex. The liver was slightly enlarged. Electrocardiograms showed evidence of a sinus tachycardia with a ventricular rate of 167. The P-R, Q-R-S, and Q-T intervals were normal. Large secondary R waves were present over the right side of the precordium in leads V1, V2, V3, and V3R, with reciprocal deep S-wave deflections over the left side of the precordium in V5 and V6. The tracing was read as showing incomplete right bundle-branch block, and right ventricular hypertrophy. Roentgenograms demonstrated evidence of severe emphysema of the right middle pulmonary lobe, with herniation of this lobe across the mediastinum *(Figs. 5 and 6).* The right upper lobe was atelectatic and the heart was displaced to the left.

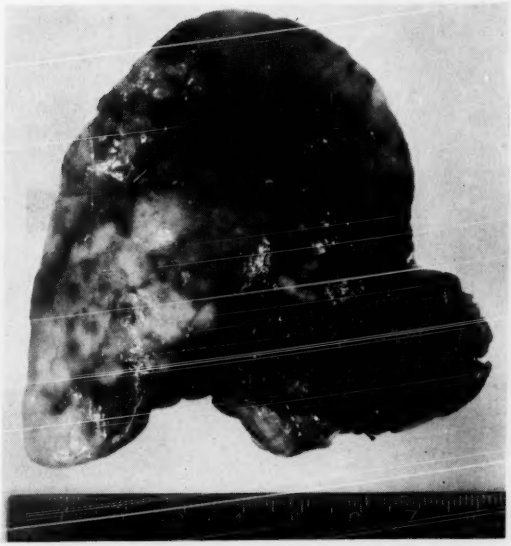

Fig. 3. Case 1. Resected right middle lobe.

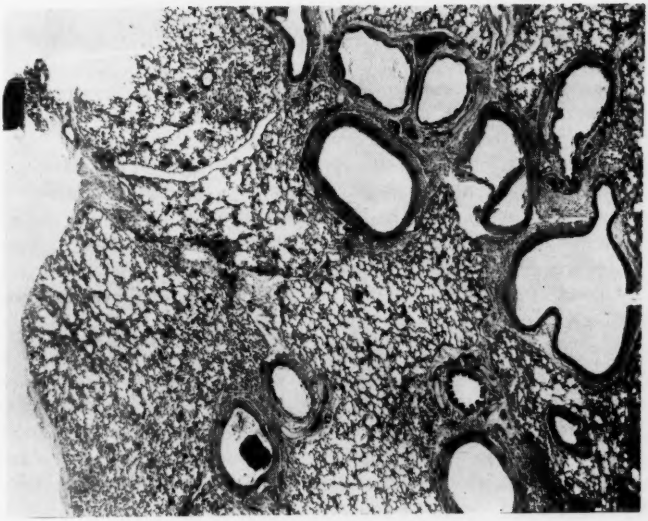

Fig. 4. Case 1. Photomicrograph of section showing widely dilated alveoli in pulmonary parenchyma; magnification X 10.

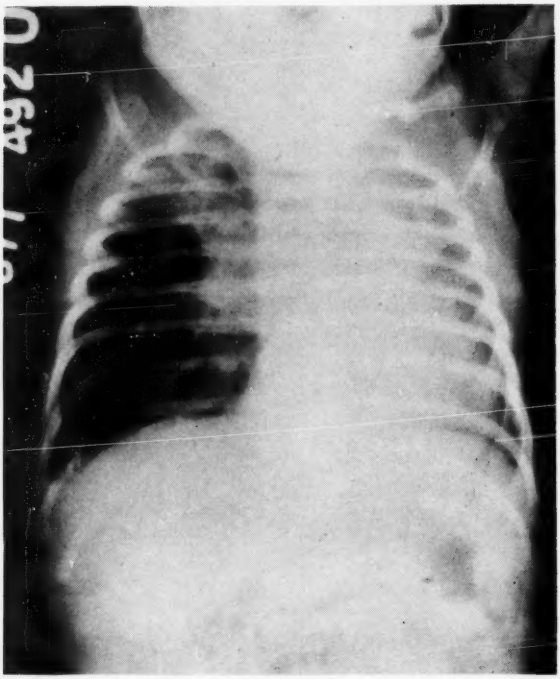

Fig. 5. Case 2. Roentgenogram of the chest, demonstrating massive emphysema of the right middle lobe, and the heart displaced to the left.

A thoracotomy was performed by Dr. Donald B. Effler of the Department of Thoracic Surgery. The greatly expanded right middle lobe could not be manually compressed, and the bronchus of the lobe appeared unusually small. The lobe was removed and the atelectatic upper and lower lobes were re-expanded. The infant tolerated the procedure well and the emergency situation was relieved.

The resected right middle lobe was immediately fixed by intrabronchial instillation with formalin solution. Dissection of the fixed specimen revealed bronchi of normal caliber and distribution. The major vessels appeared normal. Histologic sections of the tertiary bronchi and terminal bronchioles showed dilatation of these structures with moderate festooning of the ciliated epithelial lining. The bronchial cartilages and the smooth muscle of the tertiary bronchi appeared normal. The terminal bronchioles had the usual smooth muscles, but the cartilaginous plates were not observed in multiple sections. The pulmonary parenchyma contained irregularly enlarged alveolar spaces formed in part by the rupture of the alveolar septae. The distinction between alveolar ducts, alveolar sacs, and alveoli could not be made. There was no significant inflammatory reaction.

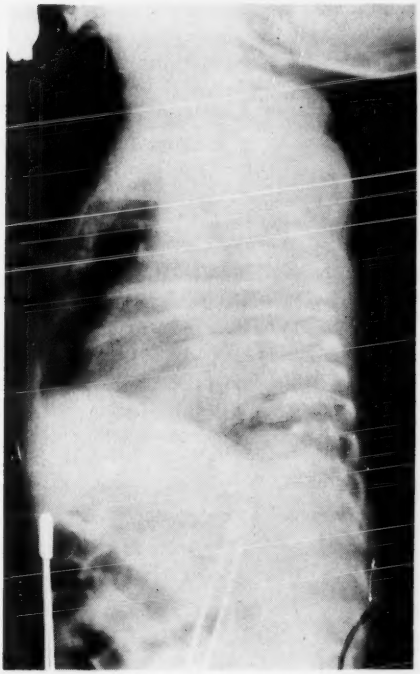

Fig. 6. Case 2. Lateral roentgenogram of the chest, demonstrating herniation of the right middle lobe in the anterior mediastinum.

At the age of two and one-half months the baby was readmitted for cardiac studies. The child had had no dyspnea, but still occasionally became cyanotic during crying. On examination the cardiac findings were essentially as previously observed. On fluoroscopy the heart appeared to be from 30 to 35 per cent enlarged. There was moderate enlargement of the right ventricular inflow and outflow tracts. The barium-filled esophagus was displaced far to the right.

Cardiac catheterization was performed in January, 1960, by Dr. Earl K. Shirey of the Department of Pediatric Cardiology and Cardiac Laboratory. Segmental hypoplasia of the right hilar pulmonary arteries could be demonstrated, and severe aneurysmal dilatation of the right main pulmonary artery. The left main pulmonary artery was normal in size, but there was hypoplasia of the distal radicals with extreme avascularity of the left upper lobe. A small interventricular septal defect was present. The status of the pulmonary valve was not ascertained as this valve could not be crossed with the catheter. The cardiac problem was considered inoperable and the child was discharged to his home in apparently good condition. Ten days later there was a sudden onset of severe cyanosis and shortness of breath after vomiting. The infant was admitted to another hospital where he died. The autopsy confirmed the findings of the cardiac catheteriza-

tion. Scattered small areas of emphysema and atelectasis were present in both lungs. No abnormality of the bronchi was described.

Case 3. A six-month-old white female infant was examined in August, 1960, because of difficulty in breathing. The pregnancy and delivery were reported to have been normal. She was said to have been well until two months of age when an upper respiratory infection developed and she suddenly became acutely ill with severe dyspnea. She was admitted to another hospital where a diagnosis of acute tracheobronchitis was made. She was treated with antibiotics, increased humidity and oxygen, and she seemed to recover. Subsequently she was hospitalized twice for similar respiratory difficulties. Roentgenograms were said to show evidence of lack of normal aeration over the right side. The left side was said to be well aerated. At the time of our initial examination the child was breathing with considerable difficulty. The chest was asymmetric, the left side being more prominent than the right side. Expiratory wheezes were prominent bilaterally. Breath sounds were decreased on the left side. Breathing was less difficult after the administration of Adrenalin, but the difference in breath sounds on the two sides persisted. Roentgenograms demonstrated evidence of a greatly increased radiolucency of the left lung field *(Fig. 7)*. The heart and the mediastinum were displaced to the right.

Bronchoscopy under general anesthesia was performed by Dr. Donald B. Effler of the Department of Thoracic Surgery. The trachea was normal; the left main bronchus

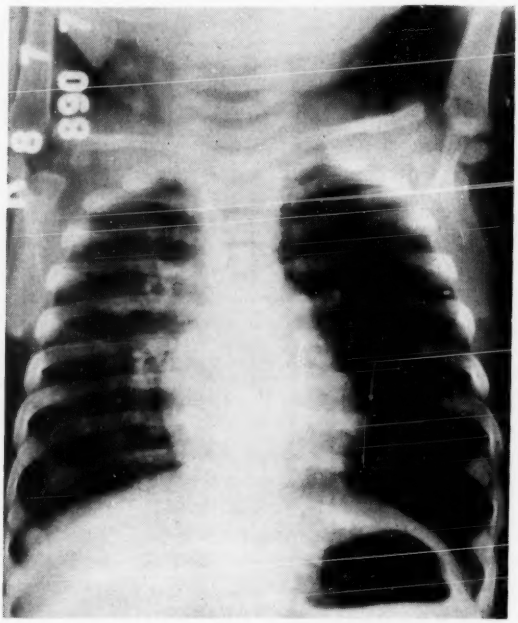

Fig. 7. Case 3. Roentgenogram of the chest, demonstrating massive emphysema of the left lung.

was erythematous with a pinhole caliber. On the next day the child's condition deteriorated rapidly, and an emergency thoracotomy was performed. The entire left lung was tremendously expanded, and it was impossible manually to compress it. When the left bronchus was transected it was observed that no air came through the bronchial stump, even under positive pressure exerted by the anesthetist. When the inflated lung was removed the child's condition promptly improved. Respirations continued to be wheezing and noisy but without dyspnea. She was discharged from the hospital 10 days after the operation.

The left lung was greatly distended but otherwise normal on gross inspection. Dissection of the bronchi and major vessels showed no abnormalities. Multiple histologic sections showed uniform distention of the tertiary bronchi and terminal bronchioles. The ciliated respiratory epithelium showed some festooning and infolding but it was less pronounced than that in the previous patient (case 2). Cartilage was present in the normal amount in the tertiary bronchi, but was not observed in the terminal bronchioles. The pulmonary parenchyma showed extremely enlarged and irregular air spaces formed sometimes by distended alveoli, and sometimes by rupture of alveolar septae *(Fig. 8)*. No significant inflammatory infiltrate was present.

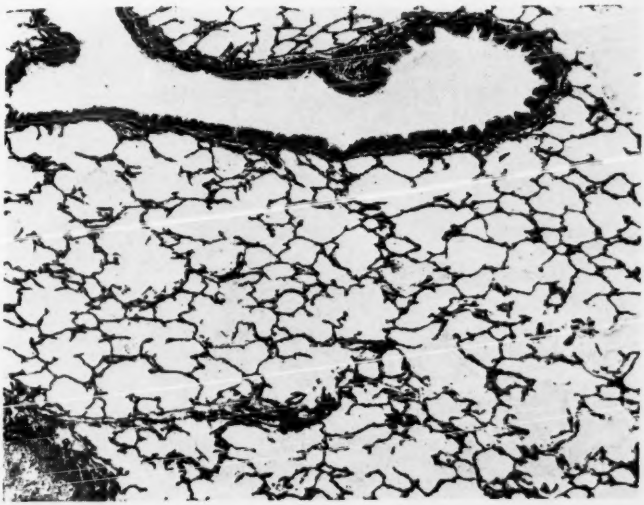

Fig. 8. Case 3. Photomicrograph of a section of the left lung, demonstrating extremely distended alveoli; magnification X 55.

Discussion

Forty-nine cases that to us represent examples of massive lobar emphysema are reported in the literature.[1-27] This small number of cases does not accurately reflect the incidence of the disease, since at least nine additional cases were mentioned by those who discussed Sloan's[1] paper on the subject. In our opinion,

the first authentic case was reported by Nelson[2] in 1932. He referred to this as a case of congenital cystic disease of the lung, and the first to be reported in America; however, his description suggests that his patient had massive lobar emphysema. Gross and Lewis[3] in 1945 performed the first successful operation for this disease in a patient who had previously been unsuccessfully operated upon because of a large mediastinal defect.

In general, massive lobar emphysema produces symptoms in early infancy. Most patients who did not have surgical treatment died.[2,4-7] It is possible that some patients with massive lobar emphysema have survived to adult life.[8,9] The early report of Wethered,[10] in 1896-1897, concerning a 51-year-old man, and that of Royes,[11] in 1938, concerning a 28-year-old man, are in our opinion of doubtful authenticity.

Lobectomy or pneumonectomy is the treatment of choice. Two patients[12] are reported to have been treated by needle aspiration, and although neither diagnosis was proved histologically, the presumptive diagnosis of each seems to be correct. In both instances needle aspiration was followed by tension pneumothorax.

Massive lobar emphysema in infants is probably caused by several factors. It would seem that obstruction of the air passages is the basic etiologic factor, although such obstruction is not always apparent. Deficiency in bronchial cartilage causing collapse of the bronchus on expiration has been the single most common associated finding;[2-6,8,13-15] stenosis of the bronchus leading to the involved lung has also been common.[3,7,16] Other possible causes include mucosal folds,[4,7,14,17] external compression of a bronchus by an abnormal blood vessel,[4,5,7,14,18] and inflammation of the bronchus.[4,19] Possibly a stenotic bronchus was left behind at the time of operation in some of the patients in whom there was no apparent cause for the disease.[1,20] Congenital heart disease, exclusive of abnormalities of the great vessels, has been described in several cases,[18,21] and was present in two of our three patients. Though relationship between the congenital heart disease and the massive lobar emphysema is not clear, it is important to decide which disease is most threatening to the life of the patient. Bolande, Schneider, and Boggs[4] described an alveolar fibrosis, in some of their patients, associated with a thickening of the supporting stroma of the alveolar walls.

The three case reports presented here demonstrated essentially the same microscopic findings in the lungs: uniform dilatation of bronchi and bronchioles, and overdistention of alveoli with rupture of alveolar septae. No cause for the emphysema was evident on study of the resected tissue. In each case stenosis of the bronchus leading to the emphysematous area was described at the time of the operation. The possibility that hypoplasia of the bronchial or bronchiolar cartilages, or hypoplasia of elastic tissue could be responsible for the emphysematous process was entertained. In all three cases, however, these structures were comparable to normal tissues removed from infants of similar ages. In no case were there significant areas of interstitial or peribronchial inflammation or fibrosis.

Summary

Massive lobar emphysema is readily diagnosed from the pathognomonic physical and roentgenographic features of the disease. Three cases of massive lobar emphysema in infants are reported. These three cases each demonstrated the presence of stenosis of the bronchus leading to the emphysematous lobe involved. The various etiologic agents described in the literature as the cause of this disease are discussed; these include hypoplasia of bronchial cartilages; valves or folds of bronchial mucosa; alveolar fibrosis; and pressure on the bronchus from abnormal blood vessels. The possibility that a stenotic bronchus may have been left behind at the time of operation in so-called "idiopathic" cases is mentioned. The treatment of this disease is surgical removal of the involved lobe, and such surgical removal is lifesaving.

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RENAL ARTERIOVENOUS FISTULA: OCCURRENCE IN RENAL-CELL CARCINOMA

Report of a Case

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RENAL arteriovenous fistula is a disorder of exceptional clinical interest because it is rare and produces unusual physical and roentgenographic findings. Of the 15 cases of arteriovenous fistula of the kidney reviewed by Scheifley, Daugherty, Greene, and Priestley,[1] in only three cases was there associated renal-cell carcinoma. We are reporting a (fourth) case in which an intrarenal fistula occurred in a renal-cell carcinoma, with the typical clinical features of the renal-vascular syndrome.

Clinical Features

Scheifley[2] states that there are four outstanding clinical features that comprise the renal-vascular syndrome typical of this unusual disease. These are: (1) *continuous bruit* heard diffusely over the upper abdomen or flank; (2) *hypertension;*† (3) *cardiomegaly,* which was present in 12 of the 15 patients; and (4) *heart failure,* which occurred in 10 patients. He points out that because of these clinical features a renal arteriovenous fistula is distinguishable from a peripheral arteriovenous fistula.

Report of a Case

A 62-year-old woman was referred to us by Dr. Adib H. Karam of Canton, Ohio, because of his diagnosis of arteriovenous fistula of the right kidney. In January, 1960, the patient experienced the sensation of a mass in the upper abdomen, but physical examination revealed only an increased resistance in this region on palpation. Ten months later she was re-examined by Doctor Karam because of a similar complaint, and at that time a mass was palpable in the right upper quadrant and flank. Further examination revealed a blood pressure of 206/110 mm. of Hg, cardiomegaly, with an apical systolic murmur, crepitant rales in both lung fields, and a loud continuous bruit over the right flank and the anterior upper abdomen.

An intravenous urogram revealed evidence of a massive right kidney with two elongated and distorted calyces *(Fig. 1).* Retrograde pyelography confirmed the presence of a large right renal mass with dilatation of all calyces and the renal pelvis, which were displaced medially along with the ureter by the mass that occupied the normal renal fossa. The chest roentgenogram revealed the heart size to be 40 per cent above

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†It is not clear to us what type of hypertension is characteristic of the syndrome.

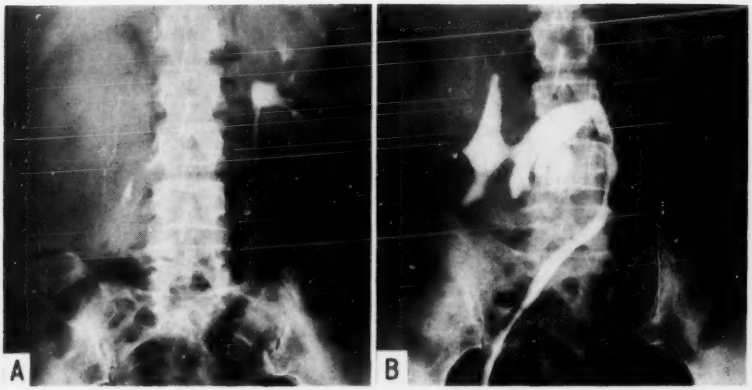

Fig. 1. A, Intravenous pyelogram showing evidence of a massive right kidney with two elongated and distorted calyces. B, Retrograde pyelogram demonstrating evidence of dilatation of all calyces and the renal pelvis with medial displacement of the right kidney and the ureter. (Courtesy of Dr. Adib H. Karam, Canton, Ohio.)

average. While in the hospital in Canton the patient received a transfusion of blood in preparation for surgical treatment, but severe pulmonary edema developed after only 200 ml. of blood had been administered; the operation was postponed. A second intravenous pyelogram in December, 1960, revealed evidence of further enlargement of the right renal mass and, because of the diagnosis of arteriovenous fistula in the kidney, she was referred to the Cleveland Clinic for angiography and possible surgery.

The main physical findings were hypertension (blood pressure ranged from 198/104 to 195/80 mm. of Hg); cardiomegaly; a large, rounded, somewhat soft mass in the right upper quadrant; and a loud continuous bruit heard most distinctly over the upper abdomen and the right flank. Examination of the ocular fundi revealed a grade 1 constriction and grade 2 sclerosis of the retinal arterioles. Results of pertinent laboratory procedures were: blood volume determination (Evans blue method)—total plasma volume of 57.2 ml. per kilogram of body weight (normal range, 37 to 39 ml.), total blood volume of 95.8 ml. per kilogram of body weight (normal range, 65 to 69 ml.), total red blood cell volume of 38.6 ml. (normal range, 27 to 29.9 ml.), and cell volume of 42 ml.; a decreased circulation time; electrocardiographic evidence of left ventricular hypertrophy. Renal angiography demonstrated evidence in the right kidney of a large mass traversed by numerous dilated vessels, and a large pool of contrast medium in the center, which was believed to represent an arteriovenous fistula within a renal tumor *(Fig. 2)*.

The patient underwent operation on January 12, 1961. Through a right subcostal incision the abdomen was examined transperitoneally, and a large retroperitoneal mass was found underneath the liver. With the hepatic flexure retracted to the midline, and the retroperitoneum open, a large, tense, renal mass covered with dilated vessels was exposed. Two large renal veins were dissected free, also an unusually large renal artery. When the renal veins, and what appeared to be the only renal artery, were

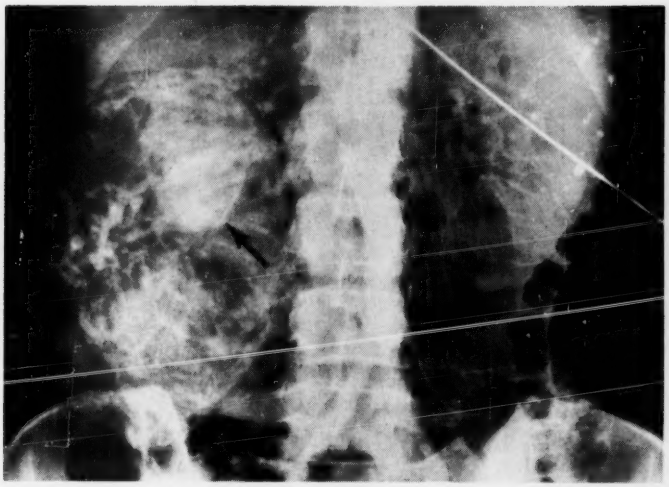

Fig. 2. Renal angiogram showing evidence of numerous dilated vessels traversing the large renal mass, and a large pool of contrast medium (arrow) representing an arteriovenous fistula.

divided, the neoplastic mass suddenly enlarged, indicating the presence of collateral circulation. The tumor was quickly removed intact and all bleeding was controlled. The patient required a transfusion of three units of whole blood to maintain a steady blood pressure during the operative procedure.

Pathologic examination revealed a kidney that weighed 640 gm., 17 cm. by 11 cm. by 6 cm., with a 7-cm. segment of ureter. In the upper pole of the kidney there was a tumor 14 cm. by 10 cm. by 5 cm. On section *(Fig. 3)* the tumor was orange, and contained cystic areas in the center of which was a rectangular-shaped cavity, 4 cm. by 5 cm. by 4 cm., lined with endothelium. It was partly filled with organized blood clot and soft tumor. Upon removal of the clot the renal artery and the renal vein were seen to enter directly into this cavity. Microscopic examination confirmed the diagnosis of renal-cell carcinoma, well differentiated, with gross intravenous invasion.

On follow-up examination the patient's blood pressure ranged from 160/100 mm. to 155/95 mm. of Hg; the bruit had disappeared; there was a noticeable decrease in cardiac size (now only 30 per cent above average) according to the chest roentgenogram; and all signs of heart failure had disappeared. Eight months postoperatively the patient is well and shows no sign of recurrent tumor.

Comment

Since our patient had the syndrome described by Scheifley[2] the diagnosis of arteriovenous fistula of the kidney was apparent from the physical examination alone. Although the intravenous urogram showed a large renal mass, the exact nature of the enlargement was not clear until the angiogram showed evidence

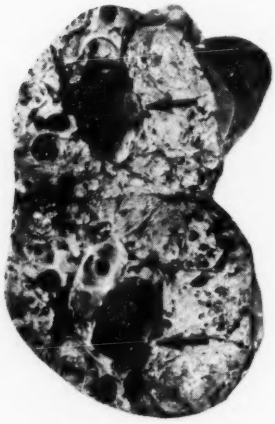

Fig. 3. Section of the neoplastic mass with an endothelial-lined cavity in the center (arrows) representing the arteriovenous fistula, and partly filled with tumor and organized blood clot.

typical of a renal tumor. The preoperative blood pressures showed a wide range of pulse pressures, from 94 to 115 mm. of Hg with variable diastolic pressures from normal to slightly elevated.

In the cases reviewed by Scheifley, Daugherty, Greene, and Priestley,[1] a considerable range of blood pressures was observed in the 12 patients whose preoperative blood pressures were recorded. Systolic hypertension without any diastolic elevation was present in seven patients, and just two of these patients were over 42 years of age. Diastolic hypertension occurred in five patients all of whom were under 40 years of age. Because the diastolic hypertension was relieved in all five patients postoperatively, as reported by Scheifley,[2] and systolic hypertension was reported in the other seven patients as in our patient, there does seem to be a relationship between hypertension and arteriovenous fistula of the kidney. However, to date there seems to be no characteristic form of hypertension in patients with renal arteriovenous fistula.

Cardiomegaly and heart failure are not peculiar to renal arteriovenous fistula, as these features can occur in a patient with a large arteriovenous fistula anywhere in the body, or with renal arterial occlusive disease and hypertension. In a patient with renal arterial occlusive disease and hypertension, a systolic bruit, heard best in or near the epigastric region, is often present. Therefore, it is important, as Scheifley[2] points out, to recognize the continuous character of the abdominal bruit, with systolic accentuation, as this appears to be the only distinctive feature associated with arteriovenous renal fistula. It would seem that the renal vascular syndrome is not such a clear-cut clinical entity as emphasized by Scheifley.[2]

The intravenous urogram is of great value in the diagnosis of arteriovenous

fistula. In all but one of the reported cases in which intravenous urography was used, evidence of an abnormality was revealed on the urogram. Renal angiography is the procedure that should establish the diagnosis beyond a doubt. In our patient not only was there evidence of urographic deformity and angiographic vascularity of a renal tumor, but also angiographic evidence of a large central pool that could result only from an abnormal arteriovenous communication. Specific laboratory tests can be used to substantiate further this diagnosis; they are: (1) blood volume determination, which should show a significant increase; (2) circulation time, which should show a decrease; and (3) catheterization of the vena cava and renal vein to demonstrate arterialization of the venous blood.

There are several varieties of arteriovenous fistula of the kidney, and they are classified according to etiopathogenesis. The *intrarenal* type is found within the kidney, and either is of congenital origin, or is acquired from direct trauma to the kidney or from breakdown of a tumor with formation of an abnormal arteriovenous communication. The *extrarenal* type is found outside the kidney, and also is either of congenital origin, possibly the result of erosion into the vein of a congenital aneurysm of a renal artery, or from traumatic injury to the renal artery and renal vein, which results in a fistula. A *postnephrectomy* type of arteriovenous fistula occurs occasionally in the stump of the renal artery and renal vein, probably where a single ligature was used to secure the renal pedicle. A search of the lierature has revealed seven reported instances of this type of fistula.[3-8] All of these types of fistula are rare,[1-9] as shown by the data in *Table 1,* but the recent

Table 1.—*Renal arteriovenous fistula. Cases include twenty-three reported,*[1-9] *and one case from the Cleveland Clinic Hospital*

Type of fistula	Number of cases		
	Total	Subtotal	
Intrarenal	9		
Congenital		3	
Acquired		6	
Trauma			(3)
Neoplasm			(3)
Extrarenal	8		
Congenital		4	
Acquired		4	
Trauma			(3)
Neoplasm			(1)
Postnephrectomy	7		

use of diagnostic aortography accounts for the fact that most of the documented cases have been discovered during the last decade.

Summary

A case report is presented of a patient who had an intrarenal arteriovenous fistula of the kidney, found within a renal-cell carcinoma, which produced a continuous abdominal bruit, systolic hypertension, cardiomegaly, and heart failure. Three other case reports of fistulas that occurred in renal tumor have been found in the literature. In our opinion the only really distinctive feature of an arteriovenous renal fistula is the continuous bruit heard over the renal area, and therefore must be differentiated from the systolic bruit of occlusive renal artery disease, of aneurysms, or of partial occlusive disease occurring in other intraabdominal vessels. The renal vascular syndrome at the present time is not a clear-cut clinical entity, paricularly since the blood pressure may be only mildly elevated in the majority of cases.

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